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10/527,525	10/14/2005	Athina Markou	TSRI 897.1	3218

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EXAMINER	
CARTER, KENDRA D	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,525	MARKOU ET AL.	
	Examiner	Art Unit	
	Kendra D. Carter	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 19-31* is/are pending in the application.

4a) Of the above claim(s) *10-15,17,19 and 23-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,16,20-22 and 27-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner acknowledges the applicant's remarks and arguments of September 7, 2007 made to the office action filed May 3, 2007. Claims 1-17 and 19-31 are pending. Claims 1-3, 9, 16, 20, 22, and 27-31 are amended and claim 18 is cancelled. Claims 10-15, 17, 19 and 23-26 are withdrawn.

In light of the cancellation of claim 18, the claim objection and 35 U.S.C. 112 and 101 rejection is withdrawn.

In light of the amendments and Applicant's arguments, the claim objection of claims 16, 22, 28, and 31; the specification objection; all 35 U.S.C. 112, first paragraph rejections of claims 1-4, 16, 18, 27-31; the 35 U.S.C. 102(b) rejection of claims 1-5,7,9,20 and 21 as being anticipated by Chiamulera et al.; the 35 U.S.C. 102(b) rejection of claims 1-8, 20, 21 and 29 as being anticipated by Adam et al.; and the 35 U.S.C. 102(b) rejection of claims 1-8, 20, 21 and 29 as being anticipated by Corsi et al. are withdrawn.

For the reasons in the previous office action and below, the Applicant's arguments of the 35 U.S.C. 102(b) rejection of claims 1-5, 20 and 21 as being anticipated by Fundytus et al. were found not persuasive, thus the rejection is upheld.

For the reasons in the previous office action and below, the Applicant's arguments of the 35 U.S.C. 103(a) rejection of claims 16, 18 and 27 as being unpatentable over Adam et al. in view of Corsi et al. were found not persuasive, thus the rejection is upheld.

For the reasons in the previous office action and below, the Applicant's arguments of the 35 U.S.C. 103(a) rejection of claims 22, 27 and 28 as being unpatentable over Chiamulera et al. in view of Adam et al. were found not persuasive, thus the rejection is upheld.

For the reasons in the previous office action and below, the Applicant's arguments of the 35 U.S.C. 103(a) rejection of claims 30 and 31 as being unpatentable over Bear et al. in view of Adam et al. were found not persuasive, thus the rejection is upheld.

Due to the amendment to the claims, the modified 35 U.S.C. 102(b) and 103(a) rejections and new 35 U.S.C. 103(a) rejections are made below.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 20 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Fundytus et al. (British Journal of Pharmacology, 1997, vol. 120, pp. 1015-1020).

Fundytus et. al. teaches a method of treating morphine withdrawal symptoms by administering an effective amount of the mGluR 1, 2, 3, and 5 antagonist α-methyl-4-carboxyphenylglycine (MCPG); see abstract paragraph 1, paragraph 2, lines 7 and 8, and page 1016, column 1, paragraph 1, last 5 lines. Since MCPG is an antagonist for the metabotropic glutamate receptor 2, 3, and 5, and treats morphine withdrawal, the teachings meet the limitation of claims 1-5, 20 and 21.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

(1) Claims 1-8, 16, 18, 20, 21 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adam et al. (US 6407,094 B1) in view of Corsi et al. (US 2003/0195139 A1) or Chiamulera et al. (Nature Neuroscience, 2001, vol. 4(9), pp. 873-874).

Adam et al. teaches compounds that act as Group II (i.e. mGluR 2 and 3) metaboltropic glutamate receptor antagonist (see column 16, lines 47 and 48) and treat conditions which lead to glutamate-deficiency functions such as nicotine addiction, opiate addiction, anxiety and depression (see column 1, lines 54-56 and column 3, lines 20-24; addresses claims 1-8, 20, 29 and 30). The antagonist can be in their pharmaceutically acceptable salts (see column 3, line 4).

Adam et al. does not teach an antagonist which modulated metabotropic glutamate receptor 5.

Corsi et al. teaches a method of treating substance dependence, wherein the substance is nicotine, opiate, cocaine, amphetamine, benzodiazepine and ethanol, comprising administering a therapeutically effective amount of an antagonist of mGluR5 (see claims 21-23; addresses claims 1-7, 20, 21, 27, 29 and 30). Depression and anxiety is also treated (see page 7, paragraph 119, line 7; addresses claims 1-3, 8, 29 and 30). The compounds can be in the form of salts (see page 3, paragraph 55, lines 1 and 2).

Chiamulera et al. teaches the significant contribution of mGlu5 receptors to the behavioral effects of cocaine addiction (see page 873, column 1, paragraph 1, last 4 lines). A decrease of self-administration of cocaine was observed with an administration of the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP); see page 873, column 2, last paragraph, lines 1-4).

Adam et al., Corsi et al., and Chiamulera et al. do not teach a combination according to any one of claims 10 to 13.

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Adam et al. and a combination according to any one of claims 10 to 13 because of the following: (1) Adam et al., Corsi et al., and Chiamulera et al. teach methods that treat addictive disorders or depression;

(2) Adam et al. teaches the treatment of addictive disorders, depression or/and anxiety with a mGluR 2 and 3 antagonist; and (3) Corsi et al. and Chiamulera et al. teach the treatment of an addictive disorder or depression with a mGluR 5 antagonist. One would be motivated to combine the two methods because although different compounds are used and antagonize different mGluR's, they both treat addictive disorders, depression or and/anxiety. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

(2) Claim 22, 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiamulera et al. (Nature Neuroscience, 2001, vol. 4(9), pp. 873-874) as applied to claims 1-8, 16, 18, 20, 21 and 29 above in view of Adam et al. (US 6407,094 B1).

Chiamulera et al. teachings are as applied to claims 1-8, 16, 18, 20, 21 and 29 above.

Chiamulera et al. does not teach the antagonist 2S-2-amino-2-(1S,2S-2carboxycyclopropane-1-yl)-3-(xanth-9-yl)propionic acid (LY341495). Also, the administration comprising: (a) administering to a subject in need thereof, an effective amount of at least one antagonist that modulates at least one of mGluR2, 3, and 5 (specifically LY341495 or/and MPEP) during a first time period, wherein the first time period is a time period wherein the subject expects to be in an environment wherein or exposed to stimuli in the presence of which, the subject habitually uses an addictive substance; and (b) administering at least one antagonist that modulates at least one of mGluR2 and/or 3 (specifically LY341495) during a second time period, wherein the second time period is a time period wherein the subject is suffering from withdrawal and/or depression, is not taught.

Adam et al. teaches compounds that act as Group II (i.e. mGluR 2 and 3) metaboltropic glutamate receptor antagonist (see column 16, lines 47 and 48) and treat conditions which lead to glutamate-deficiency functions such as nicotine addiction, opiate addiction, anxiety and depression (see column 1, lines 54-56 and column 3, lines 20-24).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Chiamulera et al. and the antagonist LY341495 because of the following: (1) both Chiamulera et. al. and Adam et al. teach

methods to treat substance abuse; (2) Adam et al. teaches the treatment of an addictive disorders or depression with a mGluR 2 and 3 antagonist; and (3) LY341495 is a well known mGluR 2 and 3 antagonist in the art (indicated by the specification page 14, paragraph 2, lines 1 and 2, and page 16, group II, line 1 and 4). One would be motivated to combine the two methods because although different compounds are used and antagonize different mGluR's, they both treat substance abuse. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Chiamulera et al. and an administration comprising: (a) administering to a subject in need thereof, an effective amount of at least one antagonist that modulates at least one of mGluR2, 3, and 5 (specifically LY341495 or/and MPEP) during a first time period, wherein the first time period is a time period wherein the subject expects to be in an environment wherein or exposed to stimuli in the presence of which, the subject habitually uses an addictive substance; and (b) administering at least one antagonist that modulates at least one of

mGluR2 and/or 3 (specifically LY341495) during a second time period, wherein the second time period is a time period wherein the subject is suffering from withdrawal and/or depression; because without unexpected results, one skilled in the art can reasonably design the period of administration.

(3) Claims 29, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bear et al. (US 6,916,821 B2) in view of Adam et al. (US 6407,094 B1).

Bear et al. teaches a method of treating anxiety comprising administering an effective amount of the Group I mGluR antagonist (i.e. mGluR 1 and 5), 2-methyl-6-(phenylethynyl)-pyridine (MPEP; see claims 1 and 2).

Bear et al. does not teach the antagonist LY341495. Also, a method wherein an antagonist of metabotropic glutamate receptor 2 and metabotropic glutamate receptor 3 (specifically LY341495) is administered when the subject experiences depression symptoms, and an antagonist of metabotropic glutamate receptor 5 (specifically MPEP) is administered when the subject experiences anxiety symptoms is not taught.

Adam et al. teaches compounds that act as Group II (i.e. mGluR 2 and 3) metaboltropic glutamate receptor antagonist (see column 16, lines 47 and 48) and treat conditions which lead to glutamate-deficiency functions such as nicotine addiction,

opiate addiction, anxiety and depression (see column 1, lines 54-56 and column 3, lines 20-24).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Bear et al. and the antagonist LY341495 because of the following: (1) Bear et al. teaches a method of treating anxiety with the mGluR 5 antagonist MPEP; (2) Adam et al. teaches a method of treating depression and anxiety with a mGluR 2 and 3 antagonist; and (3) LY341495 is a well known mGluR 2 and 3 antagonist in the art (indicated by the specification page 14, paragraph 2, lines 1 and 2, and page 16, group II, line 1 and 4). One would be motivated to combine the two methods because although different compounds are used and antagonize different mGluR's, they both treat addictive disorders or depression. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Chiamulera et al. and an

administration comprising: an antagonist of metabotropic glutamate receptor 2 and metabotropic glutamate receptor 3 administered when the subject experiences depression symptoms, and an antagonist of metabotropic glutamate receptor 5 administered when the subject experiences anxiety symptoms, because without unexpected results, one skilled in the art can reasonably design the period of administration.

Response to Arguments

Claims 1-5, 20 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Fundytus et al.

Applicant's arguments have been fully considered but they are not persuasive.

> The Applicant's argues that the reference does not teach or suggest amendments to the claims in regards to the use of both an antagonist of mGluR2/3 and an antagonist of mGluR5.

The Examiner disagrees because Fundytus et al. teaches a compound that is an antagonist to both mGluR2/3 and 5 (see abstract paragraph 1, paragraph 2, lines 7 and 8, and page 1016, column 1, paragraph 1, last 5 lines).

Claims rejected under 35 U.S.C. 103

> The Applicant argues that because the different biological activities of mGluR2/3 and mGluR5 are well known in the art, e.g., as described in the an article provided by the Applicant as Kilbride et al., Vignes et al., and Schoepp; it would be simply counter intuitive to co-administer antagonist of mGlu receptors of Group I and Group II. Therefore, one certainly would not be motivated to combine the teachings of the references cited in the Office Action. For the sake of argument, if one skilled in the art did combine the antagonist, he/she would be concerned that due to the localization of these receptors and their apparent opposing effects on glutamate signaling, co-administration of mGluR2/3 and mGluR5 antagonists would likely antagonize each other's effects to the extent that their effects are neutralized. The Applicant notes that the example is a typical "hindsight-based obviousness analysis.

The Examiner disagrees because as stated in the previous office action and above, one would be motivated to combine the two methods because although different compounds are used and antagonize different mGluR's, they both treat substance abuse, depression, and/or anxiety. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987). Additionally, Fundytus et. al. teaches a method of treating morphine withdrawal symptoms by administering an effective amount of the mGluR 1, 2, 3, and 5 antagonist α-methyl-4-carboxyphenylglycine (MCPG; see abstract paragraph 1, paragraph 2, lines 7 and 8). Also that MCPG is effective as a selective antagonist of mGluR II and III to attenuate the development of morphine dependence

(see page 1016, column 1, paragraph 1, last 5 lines). Thus, prior art has shown that the different mGluR antagonist do not neutralize or hinder each other in regards to providing therapeutic effects.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kendra D. Carter whose telephone number is (571) 272-9034. The examiner can normally be reached on 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

KDC